Zidovudine (ZDV, AZT, Retrovir)

For additional information see Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Formulations

Capsules: 100 mg

Tablets: 300 mg

Syrup: 10 mg/mL

Concentrate for injection or intravenous infusion: 10 mg/mL

Generic: ZDV capsules, tablets, and solution are approved by the Food and Drug Administration (FDA) for manufacture and distribution in the United States.

Combination Tablets:

- *With lamivudine (3TC):* ZDV 300 mg + 3TC 150 mg (Combivir)
- *With 3TC + abacavir (ABC):* ZDV 300 mg + 3TC 150 mg + ABC 300 mg (Trizivir)

Dosing Recommendations

Dose for infant <35 weeks gestation for prevention of transmission or treatment (standard neonate dose may be excessive in premature infants):
1.5 mg/kg of body weight (intravenous) or
2 mg/kg of body weight (oral) every 12 hours, increased to every 8 hours at 2 weeks of age (neonates ≥30 weeks gestational age) or at 4 weeks of age (neonates <30 weeks gestational age).

(See Perinatal Guidelines for additional information.)

Neonate/infant dose (<6 weeks of age) for prevention of transmission or treatment:
Oral: 2 mg/kg of body weight every 6 hours.

Intravenous: 1.5 mg/kg of body weight every 6 hours.
(See Perinatal Guidelines for additional information.)

Pediatric dose (6 weeks to <18 years of age):
Body surface area dosing:
Oral: 180–240 mg/m^2 of body surface area every 12 hours or 160 mg/m^2 every 8 hours.

Selected Adverse Events

- Bone marrow suppression: macrocytic anemia or neutropenia
- Nausea, vomiting, headache, insomnia, asthenia
- Lactic acidosis/severe hepatomegaly with hepatic steatosis
- Nail pigmentation
- Hyperlipidemia
- Insulin resistance/diabetes mellitus
- Lipoatrophy
- Myopathy

Special Instructions

- Give ZDV without regard to food.
- If substantial granulocytopenia or anemia develop in patients receiving ZDV, it may be necessary to discontinue therapy until bone marrow recovery is observed. In this setting, some patients may require erythropoietin or filgrastim injections or transfusions of red blood cells and platelets.

Metabolism

- Metabolized to AZT glucuronide (GAZT), which is renally excreted.

Weight-based dosing:

Body Weight	Twice-Daily Dosing*
4 kg to <9 kg	12 mg/kg
9 kg to <30 kg	9 mg/kg
≥30 kg	300 mg

**Three times daily dosing is approved but rarely used in clinical practice.*

Adolescent (≥18 years of age)/adult dose:
300 mg twice daily.

Combivir (ZDV + 3TC)
Adolescent (weight ≥30 kg)/adult dose:
1 tablet twice daily.

Trizivir (ZDV + 3TC + ABC)
Adolescent (weight ≥40 kg)/adult dose:
1 tablet twice daily.

- **Dosing of ZDV in patients with renal impairment:** Dosage adjustment is required in renal insufficiency.
- **Dosing of ZDV in patients with hepatic impairment:** Decreased dosing may be required in patients with hepatic impairment.
  - Do not use Combivir and Trizivir (fixed-dose combination products) in patients with creatinine clearance (CrCl) <50 mL/min, patients on dialysis, or patients with impaired hepatic function.

Drug Interactions (See also the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.)***:***

- *Other nucleoside reverse transcriptase inhibitors (NRTIs):* Zidovudine should not be administered in combination with stavudine because of virologic antagonism.
- *Bone marrow suppressive/cytotoxic agents including ganciclovir, interferon alpha, and ribavirin:* These agents may increase the hematologic toxicity of zidovudine.
- *Doxorubicin:* Simultaneous use of doxorubicin and zidovudine should be avoided.

Major Toxicities:

- *More common:* Hematologic toxicity, including granulocytopenia and anemia. Headache, malaise, nausea, vomiting, and anorexia. Incidence of neutropenia may be increased in infants receiving lamivudine[1].
- *Less common (more severe):* Myopathy (associated with prolonged use), myositis, and liver toxicity. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported. Fat maldistribution.
- *Rare:* Increased risk of hypospadias after first-trimester exposure to zidovudine observed in one cohort study[2].

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see http://hivdb.stanford.edu/pages/GRIP/ZDV.html).

Resistance mutations were shown to be present in 29% (5 of 17) of infants born to mothers who received zidovudine during pregnancy[3].

Pediatric Use: Zidovudine is frequently included as a component of the NRTI backbone for combination antiretroviral therapy (cART)[4-19]. Pediatric experience with zidovudine both for treatment of HIV and for the prevention of mother-to-child transmission (PMTCT) is extensive.

Perinatal trial PACTG 076 established that a zidovudine prophylactic regimen given during pregnancy, labor and delivery, and to the newborn reduced the risk of perinatal transmission of HIV by nearly 70%[20]. (Consult the Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States for further discussion on the use of zidovudine for PMTCT of HIV.)

Overall, zidovudine pharmacokinetics (PKs) in pediatric patients >3 months of age are similar to those in adult patients. Zidovudine undergoes intracellular metabolism to its active form, zidovudine triphosphate. Although the mean half-life of intracellular zidovudine triphosphate (9.1 hours) is considerably longer than that of unmetabolized zidovudine in plasma (1.5 hours), once-daily zidovudine dosing is not recommended because of low intracellular zidovudine triphosphate concentrations seen with 600-mg once-daily dosing in adolescents[21]. PK studies, such as PACTG 331, demonstrate that dose adjustments are necessary for premature infants because they have reduced clearance of zidovudine compared with term newborns of similar postnatal age[5]. Zidovudine has good central nervous system (CNS) penetration (cerebrospinal fluid-to-plasma concentration ratio = 0.68) and has been used in children with HIV-related CNS disease[22].

References

1. Nielsen-Saines K, Bryson V, Joao Y, Pilotto E, Gray JH, Theron G, Bethel J, Mofenson L and NICHD/HPTN 040 Study Group. Phase III randomized trial of the safety and efficacy of 3 neonatal ARV regimens for prevention of intrapartum HIV-1 transmission: NICHD HPTN 040/PACTG 1043. Paper presented at 18th Conference on Retroviruses and Opportunisitic Infections (CROI): February 27–March 2, 2011; Boston, MA, Abstract 124LB.
2. Watts DH, Li D, Handelsman E, et al. Assessment of birth defects according to maternal therapy among infants in the Women and Infants Transmission Study. *J Acquir Immune Defic Syndr.* 2007;44(3):299-305.
3. Kovacs A, Cowles MK, Britto P, et al. Pharmacokinetics of didanosine and drug resistance mutations in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J.* 2005;24(6):503-509.
4. Balis FM, Pizzo PA, Murphy RF, et al. The pharmacokinetics of zidovudine administered by continuous infusion in children. *Ann Intern Med.* 1989;110(4):279-285.
5. Capparelli EV, Mirochnick M, Dankner WM, et al. Pharmacokinetics and tolerance of zidovudine in preterm infants. *J Pediatr.* 2003;142(1):47-52.
6. Chadwick EG, Rodman JH, Britto P, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr Infect Dis J.* 2005;24(9):793-800.
7. Englund JA, Baker CJ, Raskino C, et al. Zidovudine, didanosine, or both as the initial treatment for symptomatic HIV-infected children. AIDS Clinical Trials Group (ACTG) Study 152 Team. *N Engl J Med.* 1997;336(24):1704-1712.
8. Jankelevich S, Mueller BU, Mackall CL, et al. Long-term virologic and immunologic responses in human immunodeficiency virus type 1-infected children treated with indinavir, zidovudine, and lamivudine. *J Infect Dis.* 2001;183(7):1116-1120.

9. King JR, Kimberlin DW, Aldrovandi GM, Acosta EP. Antiretroviral pharmacokinetics in the paediatric population: a review. *Clin Pharmacokinet.* 2002;41(14):1115-1133.

10. Luzuriaga K, Bryson Y, Krogstad P, et al. Combination treatment with zidovudine, didanosine, and nevirapine in infants with human immunodeficiency virus type 1 infection. *N Engl J Med.* 1997;336(19):1343-1349.

11. McKinney RE, Jr., Maha MA, Connor EM, et al. A multicenter trial of oral zidovudine in children with advanced human immunodeficiency virus disease. The Protocol 043 Study Group. *N Engl J Med.* 1991;324(15):1018-1025.

12. McKinney RE, Jr., Johnson GM, Stanley K, et al. A randomized study of combined zidovudine-lamivudine versus didanosine monotherapy in children with symptomatic therapy-naive HIV-1 infection. The Pediatric AIDS Clinical Trials Group Protocol 300 Study Team. *J Pediatr.* 1998;133(4):500-508.

13. Mueller BU, Nelson RPJr, Sleasman J, et al. A phase I/II study of the protease inhibitor ritonavir in children with human immunodeficiency virus infection. *Pediatrics*. 1998;101(3 Pt 1):335-343.

14. Mueller BU, Sleasman J, Nelson RP, et al. A phase I/II study of the protease inhibitor indinavir in children with HIV infection. *Pediatrics.* 1998;102(1 Pt 1):101-109.

15. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. Pediatric AIDS Clinical Trials Group 338 Study Team. *JAMA*. 2000;283(4):492-498.

16. Palacios GC, Palafox VL, Alvarez-Munoz MT, et al. Response to two consecutive protease inhibitor combination therapy regimens in a cohort of HIV-1-infected children. *Scand J Infect Dis.* 2002;34(1):41-44.

17. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med.* 1988;319(14):889-896.

18. Saez-Llorens X, Nelson RP, Jr., Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated human immunodeficiency virus type 1-infected children. The CNAA3006 Study Team. Pediatrics. 2001;107(1):E4.

19. van Rossum AM, Geelen SP, Hartwig NG, et al. Results of 2 years of treatment with protease-inhibitor--containing antiretroviral therapy in dutch children infected with human immunodeficiency virus type 1. *Clin Infect Dis.* 2002;34(7):1008-1016.

20. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med.* 1994;331(18):1173-1180.

21. Flynn PM, Rodman J, Lindsey JC, et al. Intracellular pharmacokinetics of once versus twice daily zidovudine and lamivudine in adolescents. *Antimicrob Agents Chemother.* 2007;51(10):3516-3522.

22. Pizzo PA, Eddy J, Falloon J, et al. Effect of continuous intravenous infusion of zidovudine (AZT) in children with symptomatic HIV infection. *N Engl J Med.* 1988;319(14):889-896.